

420 Rec'd PCT/PTO 13 DEC 1999

and
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(3)

CLAIMS

1. A compound comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug, or a polynucleotide encoding said NQO2 or said variant or fragment or fusion or derivative.
2. A compound according to Claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).
3. A compound according to Claim 1 or 2 wherein the target cell-specific portion is tumour cell-specific.
4. A compound according to any one of Claims 1 to 3 wherein the target cell-specific portion comprises an antibody or fragment or derivative.
5. A compound according to any one of Claims 1 to 3 wherein the target cell-specific portion comprises a macromolecule.
6. A compound according to any one of Claims 1 to 5 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.

[illegible]

Sub A2

Sub A2 7. A compound according to any one of Claims 1 to 6 comprising means for delivering said polynucleotide to said target cell.

5 8. A recombinant polynucleotide comprising a target cell-specific promoter operably linked to a polynucleotide encoding human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug.

10 9. A recombinant polynucleotide according to Claim 8 wherein said promoter is tumour cell-specific.

10. A recombinant polynucleotide according to Claim 8 or 9 comprising a polynucleotide encoding NQO2.

11. A recombinant polynucleotide according to any one of Claims 8 to 10 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. A compound according to any one of Claims 1 to 7 wherein said polynucleotide is the recombinant polynucleotide of any one of Claims 8 to 11.

13. A therapeutic system comprising a compound according to any one of Claims 1 to 7 or 12, or a polynucleotide according to any

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- | Days after hatching | Percentage of hatched larvae |
|---------------------|------------------------------|
| 0 | 0 |
| 5 | 80 |
| 10 | 95 |
| 25 | 100 |

20. A method according to Claim 18 or 19 wherein the prodrug is CB 1954 or an analogue thereof.
21. A method according to Claim 20 wherein the prodrug is CB 1954.
22. A method according to any one of Claims 18 to 21 the method further comprising administering to the patient a cosubstrate for NQO2.
23. A method according to Claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.
24. A compound according to any one of Claims 1 to 7 or 12, or a recombinant polynucleotide according to any one of Claims 8 to 10, for use in medicine.
25. Use of a compound according to any one of Claims 1 to 7 or 12, or a recombinant polynucleotide according to any one of Claims 8 to 11, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.
26. Use as defined in Claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

Sub A3
5 27. Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound according to any one of Claims 1 to 7 or 12, or a recombinant polynucleotide according to any one of Claims 8 to 11.

28. Use as defined in Claim 27 wherein the patient has a tumour to be treated.

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29. A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.
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30. A method according to Claim 29 wherein the cytotoxic drug is CB 1954 or an analogue thereof.

31. A method according to Claim 29 or 30 wherein the analogue of NRH is able to permeate the target cell membrane.

Sub A4
25 32. A method according to any one of Claims 29 to 31 wherein the target cell is a tumour.

33. A method according to any one of Claims 29 to 32 the method further comprising determining, before administering the prodrug

or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

5 34. A therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

10 35. Nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 for use in medicine.

15 36. Use of nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed.

20 37. Use as defined in Claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

25 38. Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed wherein the patient has been, is being or will be administered NRH or an analogue thereof which can pass reducing equivalents to NQO2.

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